J Neurol (2005) 252 : 1167–1170
DOI 10.1007/s00415-005-0789-9

ORIGINAL COMMUNICATION

Life-threatening orolingual angioedema during thrombolysis in acute ischemic stroke

S. T. Engelter
F. Fluri
C. Buitrago-Téllez
S. Marsch
A. J. Steck
S. Rüegg
P. A. Lyrer

Abstract *Background* Orolingual angioedema can occur during thrombolysis with alteplase in stroke patients. However, data about its frequency, severity and the significance of concurrent use of angiotensin-converting-enzyme inhibitors (ACEi) are sparse. *Objective* (1), to alert to the potentially life-threatening complication of orolingual angioedema. (2), to present CT-scans of the tongue which exclude lingual hematoma. (3), to estimate the frequency of orolingual angioedema. (4), to evaluate the risk associated with the concurrent use of ACEi. *Methods* Single center, databank-based observational study on 120 consecutive patients with i. v. alteplase for acute stroke. Meta-analysis of all stroke studies on alteplase-associated angioedema, which provided detailed information about the use of ACE-inhibitors. Across studies, the Peto odds ratio of orolingual angioedema for "concurrent use of ACEi" was calculated. *Results* Orolingual angioedema occurred in 2 of 120 patients (1.7 %, 95 % CI 0.2–5.9 %). Angioedema was mild in one, but rapidly progressive in another patient. Impending asphyxia prompted immediate intubation. CT showed orolingual swelling but no bleeding. One of 19 (5 %) patients taking ACEi had orolingual angioedema, compared to 1 of 101 (1 %) patients without ACEi. Medline search identified one further study about the occurrence of alteplase-associated angioedema in stroke patients stratified to the use of ACEi. Peto odds ratio of 37 (95 % CI 8–171) indicated an increased risk of alteplase-triggered angioedema for patients with ACEi ($p < 0.001$). *Conclusion* Orolingual angioedema is a potentially life-threatening complication of alteplase treatment in stroke patients, especially in those with ACEi. Orolingual hematoma as differential diagnosis can be excluded by CT-scan.

Key words thrombolysis · acute ischemic stroke · tissue plasminogen activator · complication · angioedema

Received: 8 November 2004
Received in revised form: 8 December 2004
Accepted: 21 December 2004
Published online: 27 September 2005

S. T. Engelter, MD (✉) · F. Fluri, MD · A. J. Steck, MD · S. Rüegg, MD · P. A. Lyrer, MD
Neurological Clinic and Stroke Unit
University Hospital Basel
Petersgraben 4
4031 Basel, Switzerland
Tel.: +41-61/265-2525
Fax: +41-61/265-5644
E-Mail: sengelter@uhbs.ch

C. Buitrago-Téllez, MD
Dept. of Radiology
University Hospital Basel, Switzerland

S. Marsch, MD
Intensive Care Unit
University Hospital Basel, Switzerland

Introduction

Orolingual angioedema can occur during alteplase therapy in patients with acute ischemic stroke [3, 6]. In most patients, orolingual angioedema was mild and transitory [3]. In contrast to intracerebral hemorrhage as a major concern in thrombolysis, life-threatening orolingual angioedema as a complication of alteplase treatment in stroke patients is hardly mentioned. Alteplase-triggered angioedema seems to be associated with angiotensin-converting enzyme (ACE) inhibitors [3]. However, alteplase-triggered angioedema has also been reported in patients never exposed to ACE-inhibitors [6]. In view of these data, the present report has the following objectives. First, to warn of the potentially life-threatening complication of orolingual angioedema. Second, to present CT images of the tongue which exclude lingual hematoma despite oral bleeding. Third, to estimate the frequency of orolingual angioedema among stroke pa-

tients treated with alteplase. Fourth, to estimate the risk associated with the concurrent use of ACE-inhibitors.

Methods

The Basel Stroke Unit program includes a prospective stroke registry and defines stroke management pathways. Intravenous thrombolysis with alteplase has been applied to all patients fulfilling criteria adapted from the NINDS-trial. Alteplase administration and monitoring for 24-hours has been performed on an intensive care unit (ICU) for all patients. For each patient, demographic and clinical data including concurrent medication, complications, and functional outcome have been recorded in the thrombolysis databank. Based on these data, we determined the percentage (± 95 %-CI) of orolingual angioedema. Fisher's exact test was used to compare the frequency of orolingual angioedema among patients who concurrently took ACE-inhibitors versus those who did not.

In addition, we performed a Medline search to identify all studies reporting on the frequency of orolingual angioedema in alteplase-treated stroke patients with additional information about the concurrent use of ACE-inhibitors. We calculated a weighted estimate of the odds of alteplase-triggered angioedema comparing patients with versus without concurrent ACE-inhibitors across studies using the Peto odds ratio method.

Results

During 6 years (June 1998 to May 2004), 120 stroke patients received alteplase. Mean age was 66 (± 14) years. Median NIH-stroke-scale-score was 14. Nineteen patients (16 %) took ACE-inhibitors, 31 (26 %) betablockers, 14 (12 %) calcium channel blockers, 13 (11 %) AT2-blockers, and 53 (44 %) antiplatelets, when receiving alteplase. Orolingual angioedema was observed in 2 of 120 patients (1.7 %, 95 %-CI 0.2–5.9 %). In both patients, orolingual angioedema was bilateral and occurred 30 minutes after alteplase application had started. In one patient, orolingual angioedema was mild and disappeared spontaneously within three hours. In another patient, lingual swelling was rapidly progressive. Impending asphyxia prompted immediate intubation. The observation of mild bleeding in the mouth pointed to the possibility of lingual hematoma. CT confirmed angioedema and excluded lingual hematoma (Fig. 1). Steroids and antihistaminics were used and orolingual angioedema decreased gradually. In both patients, CT prior to thrombolysis showed early signs of insular infarction on the left.

The patient with severe angioedema took ACE-inhibitors. The one with mild angioedema did not. The frequency of orolingual angioedema among patients taking ACE-inhibitors was 5 % (1/19) compared with 1 % (1/101) in patients without concurrent use of ACE-inhibitors ($p = 0.1$).

Medline search revealed one further study with detailed information about the use of ACE-inhibitors for all alteplase-treated stroke patients [3]. Across both studies, the Peto odds ratio of 37 (95 %-CI 8–171) indicated an increased risk of alteplase-triggered angioedema for patients taking ACE-inhibitors ($p < 0.001$)(Fig. 2).

Discussion

Our study yielded the following results. (1) Orolingual angioedema can become a life-threatening complication of alteplase therapy for stroke. (2) Lingual hematoma as important differential diagnosis can be excluded by CT. (3) Orolingual angioedema occurred in 1–2 % of alteplase-treated stroke patients. (4) Patients taking ACE-inhibitors exhibit an increased risk of orolingual angioedema during alteplase treatment for acute stroke.

Orolingual angioedema, though mild and spontaneously reversible in most patients [3] can have a rapidly progressive course. Upper airway obstruction with impending asphyxia can occur suddenly, requiring urgent intubation or even cricothyroidotomy. As a practical consequence of this potentially life-threatening complication, we continue administering alteplase in stroke patients exclusively in the ICU, where close monitoring as well as immediate intubation is always available.

Lingual hematoma as the most important differential diagnosis of acute tongue swelling during thrombolysis was observed during alteplase therapy. However, imaging data were missing in this report [7]. To our knowledge, this is the first report of CT findings of the tongue, which excluded lingual hematoma and confirmed angioedema as underlying pathology for the clinically observed lingual swelling in alteplase-treated stroke patients.

We observed orolingual angioedema during alteplase therapy for stroke with a frequency of 1.7 %. Because of a wide 95 % confidence interval (0.2–5.9 %) the true incidence rate might even be higher. Others have reported similar frequencies ranging from 0.9 % [6] to 5.1 % [3]. Although these frequencies may reflect a publication bias, the risk of orolingual angioedema during alteplase treatment for stroke is likely to be higher than the < 0.02 % frequency estimated for the same agent used in myocardial infarction [2]. Such a discrepancy may be explained by brain infarcts causing injury to the autonomic nervous system which enhances the susceptibility to angioedema [3, 6]. Such a hypothesis would also explain why angioedema in several patients (but not in ours) was unilateral [3, 5]. The observation that both of our patients had early signs of insular infarction corroborates previous findings indicating that ischemic injury of the insular cortex may play a role in the genesis of angioedema [3].

Orolingual angioedema associated with alteplase which is a recombinant tissue plasminogen activator (rtPA) has been attributed to an increased bradykinin production [3, 4]. Tissue plasminogen activator converts

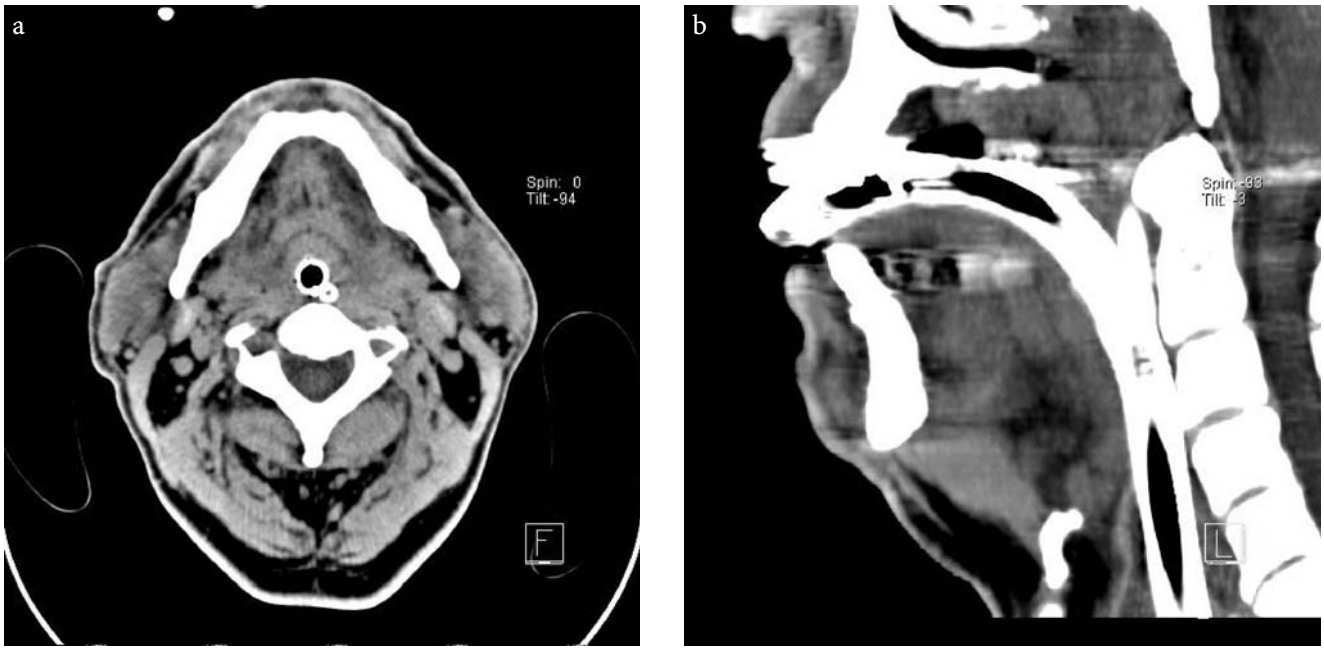

Fig. 1 (**a**) transaxial CT at the level of the base of the tongue shows diffuse swelling of the mouth floor, base of the tongue and oropharynx. Hyperdense areas or anatomical distortion indicating hemorrhage were absent. Note the minimal space for the endotracheal tube. (**b**) Sagittal midline 2D multiplanar reconstruction of multislice CT scan shows diffuse swelling of the tongue up to the epiglottic level

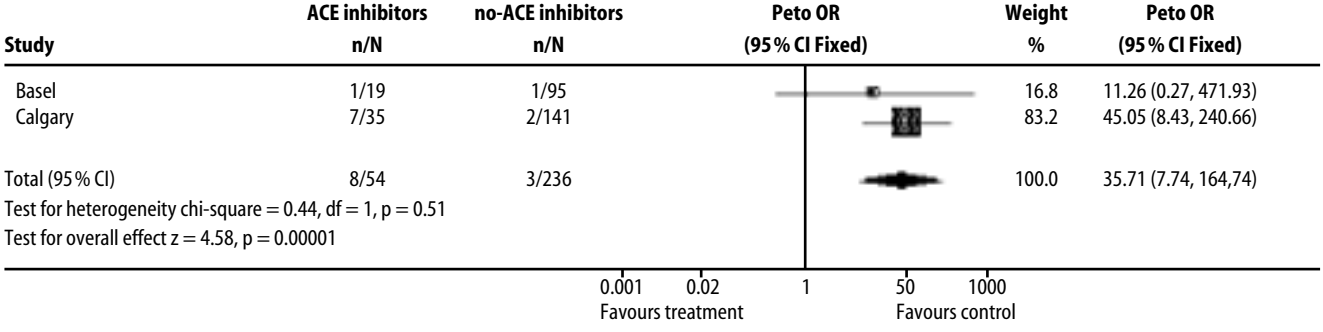

Fig. 2 Peto odds ratio for orolingual angioedema during alteplase-treatment in acute stroke comparing patients with ACE-inhibitors versus those without

plasminogen to plasmin, which in turn cleaves bradykinin from high-molecular-weight kininogen [4]. Angioedema associated with ACE-inhibitors is caused by a reduced clearance of bradykinin due to ACE-inhibitors. In addition, neurokinins (e. g. substance P) are also mediators of angioedema formation and airway inflammation [1]. By the use of ACE-inhibitors, the level of neurokinins increases. Furthermore, neurokinins, bradykinin as well as its active metabolite des-Arg^9-bradykinin are likely to interact in processes leading to angioedema (i. e., vasodilatation, plasma extravasation, mucosal edema) [1]. In patients who take ACE-inhibitors and receive alteplase treatment, the combination of rtPA-mediated increase in bradykinin release [4] and an ACE-inhibitor-mediated decrease in bradykinin metabolism together with increased neurokinin levels may thus increase the probability for angioedema. These pathophysiological considerations might explain why ACE-inhibitors increased the risk of orolingual angioedema in alteplase-treated stroke patients [3], as indicated by the high odds ratio [37]. However, this number should be interpreted cautiously, because its calculation is based on just two studies. Furthermore, the 95% confidence interval is wide [8–171]. Thus, future studies are warranted to improve the accuracy of risk estimation for angioedema in stroke patients with ACE-inhibitors who receive alteplase.

In conclusion, alteplase-triggered orolingual angioedema can become life-threatening and is not a negligible complication in stroke patients, especially in

those taking ACE-inhibitors. Orolingual hematoma as differential diagnosis can be excluded by CT.

Acknowledgement The study was supported by the Basel 'Hirnschlag-[Stroke]-Fonds'.

References

1. Campos MM, Calixto JB (2000) Neurokinin mediation of edema and inflammation. Neuropeptides 34:314–322
2. Canadian Pharmacists Association (1999) In: Gillis CM, Welbanks L, Bergeron D, Cormier-Boyd M, Hachborn F, Jovaisas B, et al. (eds). Compendium of pharmaceuticals and specialties. 34th ed. Ottawa, Canada: Canadian Pharmacists Association, pp 31–34
3. Hill MD, Lye T, Moss H, Barber PA, Demchuk AM, Newcommon NJ, Green TL, Kenney C, Cole-Haskayne A, Buchan AM (2003) Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke. Neurology 60:1525–1527
4. Molinaro G, Gervais N, Adam A (2002) Biochemical basis of angioedema associated with recombinant tissue plasminogen activator treatment: an in vitro experimental approach. Stroke 33:1712–1716
5. Pancioli A, Brott T, Donaldson V, Miller R (1997) Asymmetric angioneurotic edema associated with thrombolysis for acute stroke. Ann Emerg Med 30(2):227–229
6. Rudolf J, Grond M, Schmulling S, Neveling M, Heiss W (2000) Orolingual angioneurotic edema following therapy of acute ischemic stroke with alteplase. Neurology 55:599–600
7. Shaps HJ, Snyder GE, Sama AE, Rudolph GS (2001) Airway compromise secondary to lingual hematoma complicating administration of tissue plasminogen activator for acute ischemic stroke. Ann Emerg Med 38:447–449